REMARKS

I. Preliminary Remarks

Claims 1-19 are currently pending in the present application. In the Office Action dated November 17, 2005, claims 1-19 were rejected. More particularly, claims 1-19 were rejected for indefiniteness under 35 U.S.C. §112, second paragraph. Claims 1-3 and 13-19 were rejected for obviousness under 35 U.S.C. §103(a). Claims 1-19 were rejected under the judicially created doctrine of obviousness-type double patenting. Claims 4 and 5 were also rejected under 35 U.S.C. §101 for being drawn to natural non-patentable polynucleotides. The Office Action also made various objections to informalities.

Applicants have amended claim 1 so that it recites a bactericidal/permeability-increasing protein (BPI) deletion analog consisting of amino acid residues 10 through 193 of mature human BPI (SEQ ID NO:2), wherein a cysteine residue at position 132 is replaced by a different amino acid. The amendment is supported throughout the specification including, for example, by SEQ ID NO:2. This amendment is not being made in response to any statutory requirement of patentability, but rather to more clearly distinguish the present claims from claims in the parent cases (particularly U.S. Patent Nos. 6,013,631 and 6,087,126). In the parent cases, similar claim language was found allowable and supported by the specification, in that claims were amended in the parent cases to state that the amino acid at position number 185 is selected from lysine and glutamic acid.

II. Withdrawal of the Restriction Requirement

Applicants acknowledge with thanks that the Office Action of November 17, 2005 has withdrawn the previous restriction requirement. Applicants agree this is proper since it is not unduly burdensome for the Office to search and examine all of the pending claims together.

III. Objections to the Specification

The Office Action of November 17, 2005 objected to the specification based on various informalities. The Office Action indicated that the abstract should include the steps in the claimed methods. Applicants have amended the abstract so that it recites methods for administering a BPI protein product to a subject comprising administering a composition comprising the BPI deletion analog and a pharmaceutically-acceptable diluent, adjuvant, or carrier to the subject.

The Office Action also objected to the specification as having embedded sequences at pages 2 and 31, and Figure 3, which require sequence identifiers from the "Sequence Listing". Applicants are willing to amend the specification to include sequence identifiers; however, it does not appear that there are any "embedded sequences" requiring sequence identifiers at pages 2 and 31, and there is no Figure 3 in the application. Applicants respectfully request clarification of this objection in the next Office Action, if necessary.

The Office Action also requested that Applicants update the continuing application data starting on the first line of the first page. Applicants have amended the

specification to update the continuing application data. Each of the three parent cases has now issued as a U.S. Patent.

IV. Rejection Based Upon 35 U.S.C. §101

The Office Action rejected claims 4 and 5 under 35 U.S.C. §101 because those claims recite "A polynucleotide" which reads on the natural, non-patentable, state of the polynucleotide. The Office Action stated that the rejection would be obviated by the insertion of language indicating that the polynucleotide was isolated and/or purified. Applicants have amended claims 4 and 5 so that they recite "An isolated polynucleotide", thereby obviating this rejection.

V. Rejections Based Upon 35 U.S.C. §112

The Office Action rejected claims 1-19 under 35 U.S.C. §112, second paragraph, as indefinite. The Office Action stated that claims 1-19 were indefinite because the claims describe a sequence that requires reference to a sequence identifier. Applicants submit that the amino acid sequence of human BPI, including allelic variants thereof, is well known in the art and clearly described, for example, in U.S. Patent No. 5,420,019, which is incorporated by reference in the present application. Nonetheless, in order to expedite prosecution of the present application, Applicants have amended claim 1 to recite a sequence identifier.

The Office Action also stated that claim 6 is indefinite for reciting "...the twenty seven amino acid leader sequence of BPI." The Office Action stated that it is not clear which BPI this is. Applicants have amended claim 6 to refer to amino acid residues -27 through -1 of SEQ ID NO: 2, thereby obviating the indefiniteness rejection.

The Office Action also stated that claims 17-19 are indefinite because they use the term "improved method". Applicants have amended claims 17-19 to remove the term "improved", so that those claims refer to "a method". Applicants submit that these amendments obviate the indefiniteness rejections.

VI. Rejections Based Upon 35 U.S.C. §103(a)

In the Office Action dated November 17, 2005, claims 1-3 and 13-16 were rejected under 35 U.S.C. §103(a) for obviousness over Horwitz et al., *Protein Expression Purification*, 8:28-40 (1996) (hereafter "Horwitz") in view of Capodici et al., *J. Immunology*, 156:4789-4796 (1996) (hereafter "Capodici") and further in view of Little, U.S. Patent No. 5,652,332 (hereinafter "Little"). The Office Action stated that Horwitz teaches a BPI analog containing amino acid residues 1 through 193 of BPI with a C132A modification (also described herein as $rBPI_{21}$ or rBPI(1-193)C132A), and that Capodici teaches that *in vitro* transcription/translation products of DNAs encoding amino acids 1-193 and amino acids 13-193 of BPI both bound LPS. The Office Action stated that it would have been obvious from Capodici that any of the first 12 amino acids of $rBPI_{21}$ could be deleted without affecting function. The Office Action also stated that Little teaches the use of pharmaceutically acceptable carriers with BPI protein products.

The Office Action also rejected claims 1-3 and 13-19 under 35 U.S.C. §103(a) for obviousness over Horwitz in view of Capodici and Little, and further in view of McGregor *et al.* U.S. Patent No. 5,488,034 (hereinafter "McGregor"). The Office Action stated that McGregor teaches administration of BPI protein wherein the BPI had a mutation at position 132, where cysteine is replaced with alanine. The Office Action stated that the

process of claims 17-19 would have been obvious since the combined references teach "administering BPI modified in a manner identical if not similar to that recited in the claims" in an appropriate carrier (see, e.g., McGregor, col. 3 and example 4 *et seq.*).

The Office Action acknowledges that none of the cited references discloses a BPI deletion analog consisting of amino acid residues 10 through 193 of human BPI. The references fail to teach the specific BPI deletion analog as claimed by both the original and amended claims.

Although the Office Action relied on Capodici to assert that deletion of the N-terminal 12 amino acids of BPI did not diminish BPI function, Capodici employed a qualitative LPS-binding assay and used unpurified *in vitro* transcription/translation products that may produce inaccurate results. For example, Capodici itself shows inconsistency among activity results for polypeptides produced by host cells and polypeptides produced by *in vitro* transcription/translation. Page 4792, first column, states that "a C175S mutant of BPI was recovered in cellular acid extracts (Fig. 5A, lane 2) and the extracellular medium (Fig. 5A, lane 5; Fig. 1B, lane 2), and in both fractions exhibited an antibacterial potency only slightly less than that of wild-type BPI (Fig. 2D)." In contrast, Figure 6 (legend) shows that the C175S mutant displayed essentially no LPS-binding activity.

Furthermore, Capodici does not teach that removal of amino acids 1-12 from a BPI fragment resulted in any functional advantages, and Capodici provided no specific motivation to remove amino acids 1-9, rather than amino acids 1-12, of a BPI(1-193) fragment. Applicants directly compared the *in vivo* effects of $rBPI_{21}$ to rBPI(10-193)C132A and observed unexpected advantageous results with the latter. Example

8C (pages 25-26 of the present application), using a mouse endotoxin challenge model, showed that rBPI(10-193)C132A appeared to be at least two-fold more potent ($p<0.05$) than $rBPI_{21}$ in two studies. In Example 8E (pages 27-28) and Figure 1, additional *in vivo* experiments comparing the hypotensive response in rats following administration of rBPI(10-193)C132A versus administration of $rBPI_{21}$ indicated that rBPI(10-193)C132A avoided or reduced the transient decrease in blood pressure observed with doses of $rBPI_{21}$. These unexpected advantageous properties of rBPI(10-193)C132A are not suggested by any of the cited art and were clearly attributable to the N-terminal truncation of amino acids 1-9 because the only difference between the two polypeptides being compared was the presence or absence of amino acid residues 1-9.

Accordingly, Applicants submit that claims 1-3 and 13-19 are not rendered obvious by the prior art, and the rejection of those claims should be withdrawn.

VII. Rejections Based Upon Obviousness-Type Double Patenting

Claims 1-19 were rejected under the judicially created doctrine of obviousness-type double patenting. More particularly, claims 1-3 and 13-16 were rejected for obviousness-type double patenting over claims 1-7 of U.S. Patent No. 6,013,631, claims 4-12 were rejected for obviousness-type double patenting over claims 1-10 of U.S. Patent No. 6,087,126, and claims 17-19 were rejected for obviousness-type double patenting over claims 1-39 of U.S. Patent No. 6,599,880.

In order to expedite the allowance and issuance of the present application, Applicants are submitting a Terminal Disclaimer for the present application with respect to U.S. Patent No. 6,013,631, U.S. Patent No. 6,087,126, and U.S. Patent No. 6,599,880.

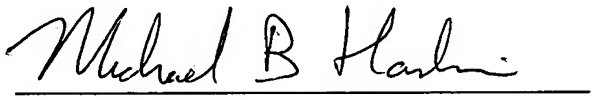
Applicants' submission does not constitute an admission as to the accuracy or effect of the obviousness-type double patenting rejections. The submission of the Terminal Disclaimers overcomes the obviousness-type double patenting rejections of claims 1-19.

VIII. Conclusion

In view of the amendments and remarks made herein, Applicants submit that claims 1-19 are in condition for allowance. The Examiner is invited to telephone the undersigned to discuss any questions or be of any assistance to the Examiner in the reconsideration and allowance of this case.

Respectfully submitted,

Date: March 16, 2006



Michael B. Harlin
Registration No. 43,658

McAndrews, Held & Malloy, Ltd.
500 West Madison Street, 34th Floor
Chicago, Illinois 60661
Telephone: (312) 775-8000
Facsimile: (312) 775-8100